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Workshop/poster session 8: Pathogen evasion of the host cytokine response

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SARS-coronavirus inhibits interferon induction both at pre- and post-transcriptional levels

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Severe acute respiratory syndrome (SARS) is caused by a novel coronavirus termed SARS-CoV. We have previously shown that SARS-CoV has the ability to prevent the activation of IRF-3, thus inhibiting the synthesis of the antiviral type I interferons (IFN) such as IFN-beta. Several unspecific as well as IRF-3-specific IFN antagonists of SARS-CoV have recently been identified. However it was also suggested that cells may simply be unable to detect the infection, because the virus is hiding in compartments surrounded by a double layer of membranes. Here, we demonstrate that this balance of viral hiding and preventing the activation of the cellular defense mechanisms can be tipped by pretreating cells with small amounts of IFN-alpha. By exploiting this priming effect, we were able to achieve an induction of IFN-beta and several other antiviral genes in response to infection with SARS-CoV. Surprisingly however, neither IFN nor other cytokines were secreted into the supernatant, although the corresponding mRNAs were clearly upregulated, whereas expression of endogenous proteins remained unaffected. These findings indicate that SARS-CoV does also inhibit a step following transcription of antiviral genes, most probably by inhibiting the secretion of cellular proteins. Thus, SARS-CoV displays a wide range of measures to counteract the type I IFN response at multiple levels.

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Reovirus inhibits interferon signaling through a novel mechanism involving nuclear accumulation of IRF9

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The secreted cytokine interferon alpha/beta (IFN-α/β) binds its receptor to activate the Jak-STAT signal transduction pathway, leading to formation of the heterotrimeric IFN-stimulated gene factor 3 (ISGF3) transcription complex, for induction of IFN-stimulated genes (ISGs) and establishment of an antiviral state in the cell. Many viruses have evolved countermeasures to inhibit this IFN pathway, thereby subverting the innate antiviral response. Here we demonstrate that the mildly myocarditic reovirus, T1L, but not the non-myocarditic reovirus T3D, represses IFN induction of a subset of ISGs, and that this repressor function is determined by the M1 gene of T1L. Expression of the T1L-M1 gene dramatically inhibits IFN-β-induced reporter gene expression. Surprisingly, T1L infection does not degrade components of the ISGF3 complex or interfere with STAT nuclear translocation as do other viruses. Instead, infection with T1L or viruses containing the T1L-M1 gene results in nuclear accumulation of IRF9; an effect not previously described for any virus. The M1 gene has also previously been identified as a determinant of virus strain-specific differences in the IFN response, and the M1 gene and the IFN response have been identified as determinants of virus strain-specific differences in induction of murine myocarditis. Here, we find that viral induction of myocarditis is associated with expression of the repressor function, providing new insights into the determinants of viral myocarditis. Together the data provide the first report of an increase in IRF9 nuclear accumulation associated with viral subversion of the IFN response, and provide evidence that virus strain-specific differences in IFN antagonism are a determinant of disease.

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Innate immune response triggered by influenza A virus is negatively regulated by suppressor of cytokine signaling (SOCS)1 and SOCS3 through a RIG-I/IFNAR1-dependent pathway

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Influenza A virus (IAV) triggers a contagious respiratory disease that produces considerable lethality. Although this lethality is likely due to an excessive host inflammatory response, the negative feedback mechanisms aimed to regulate such response are unknown. Here, we investigated the role of the eight "suppressor of cytokine signaling" (SOCS) regulatory proteins in IAV-triggered cytokine expression in human respiratory epithelial cells. SOCS1–SOCS7, but not cytokine inducible src homology 2-containing protein (CIS), are constitutively expressed in these cells and only SOCS1 and SOCS3 expression is up-regulated upon IAV challenge. Using distinct approaches affecting the expression and/or the function of the IFNa/ß receptor (IFNAR)1, the viral sensors TLR3 and RIG-I as well as MAVS (a RIG-I signaling intermediate), we demonstrated that SOCS1 and SOCS3 up-regulation requires a TLR3-independent, RIG-I/MAVS/IFNAR1-dependent pathway. Importantly, using vectors overexpressing SOCS1 and SOCS3, we revealed that while both molecules inhibit antiviral responses, they differentially modulate inflammatory signaling pathways.

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PML is cleaved and degraded in EMCV-infected cells

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The interferon-induced ProMyelocytic Leukaemia (PML) protein localises both in the nucleoplasm and in matrix-associated multi-protein complexes known as nuclear bodies (NBs). NBs are disorganised in acute promyelocytic leukemia or during some viral infections, suggesting that PML NBs could be a part of cellular defence mechanism. PML is expressed as a family of isoforms (PML I–VII) as a result of alternative splicing,from a single gene. We have shown that PMLIII isoform expression in CHO and U373MG cells confers resistance to Vesicular Stomatitis Virus, influenza virus and Human Foamy Virus but not to EncephaloMyoCarditis Virus (EMCV). EMCV counteracts this antiviral defense by inducing its degradation both in cells stably expressing PMLIII or in IFN-treated cells. Indeed, EMCV infection induced PML transfer from the nucleoplasm to the nuclear matrix and PML SUMOylation. Cleavage of PML is carried out by the EMCV 3C protease which colocalises with PML within the NBs. Degradation of PMLIII during EMCV infection required its RING domain, its C-terminal region and its sumoylation, this process occurs in a proteasome- and caspase-dependent manner. EMCV-induced PML degradation may be a mechanism to antagonize IFN-induced antiviral state.

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